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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/308,829	07/14/99	SCHLIEVERT	P 600.347USWO

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EXAMINER	
HINES, J	
ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 06/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/308,829	Schlievert et al.
Examiner	**Group Art Unit**
Ja-Na Hines	1641

☒ Responsive to communication(s) filed on *Mar 10, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-17* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Amendment Entry

1 The amendment filed March 10, 2000 has been entered. Claims 1, 11-12 and 15-16 have been amended. Claim 17 has been amended. Claims 1-17 are pending in this Office Action.

Claim Objections

2. Claim 17 is objected to because of the following informalities: the claim uses the word "specie". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-10, 13-14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al. Goshorn et al., teaches the nucleotide sequence of Streptococcal Pyrogenic Exotoxin type C and found that the SPE-C had the greatest sequence homology with SPE-A (abstract). SPE-C is a member of a family of biologically and biochemically related toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* (page 2518). The toxins occur in three serologically distinct forms, A, B and C and have been

associated with streptococcal toxic shock-like diseases (page 2518). The authors have also previously reported the cloning of the gene for SPE-C where the gene was localized, DNA fragments were ligated to bacteriophages, transformed in *E. coli* and recombinant phages were selected (page 2518). Deletion subclones were obtained using exonuclease activity and further suggest using site-directed mutagenesis to analyze the toxin (page 2518). The SPE-C amino acid sequence was found to be highly related to SPE-A sequences and found to have a high degree of similarity by allowing conservative amino acids changes (page 2519, Table 1 and Figure 2). The amino acid alignments reveal some clusters of conservation particularly in the carboxyl halves of the proteins, however the regions may represent biologically important sites necessary for the structural integrity of the proteins (page 2519). However, Goshorn et al., does not specifically teach mutant proteins.

Hartwig et al.., teaches streptococcal pyrogenic exotoxin A (SPEA) is an important pathogenicity factor of group A streptococci and it is a member of the family of super antigens (abstract). The authors have generated nine mutant SPEA molecules by substituting amino acids in the regions of homology between different streptococcal and staphylococcal superantigens (abstract). Additional mutants were also created by deletion of the 10 N-terminal amino acids (abstract). Several mutations created lead to loss of function but do not affect the binding of neutralization antibodies (page 869). The Methods section teaches introduction of single point mutations into the speA gene and the expression and purification of the recombinant SPEA proteins (page 870). Figure 1 shows the location of amino acids substitutions in the different

mutants of SPEA. Figure 3 shows the mitogenic activity of mutant SPEA molecules. Some of the results show that the replacement of amino acid residues within the conserved regions of SPEA does not affect the expression of two individual neutralizing epitopes (page 874). Other studies using mutagenesis of toxin genes had been published, where some have substituted with cysteine or alanine (page 874). The residue Lys-138 is not part of the alpha5 groove and therefore is not directly involved in the class II interaction. The mutants are still able to induce such neutralizing antibodies and could be used for vaccination purposes (page 875).

Therefore, it would have been obvious at the time of applicants invention to have used the SPE-C which has the greatest sequence homology with SPE-A as taught by Goshorn et al., with the mutations and vectors taught by Hartwig et al., because Hartwig et al., teaches mutant SPE molecules by substituting and deleting amino acids where several mutations created lead to loss of function but do not affect the binding of neutralization antibodies.

4. Claims 11-12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Hartwig et al., in further view of Leung et al. Goshorn et al., and Hartwig et al., have been discussed above, however, they do not use of toxins comprised within a vaccine. Leung et al., teaches that streptococcal exotoxins or homologous exotoxins may be involved in the pathogenesis of acute Kawasaki syndrome and it has been found that Kawasaki and its associated antigens are produced by bacteria which also produce the toxic shock syndrome toxin (TSST-1) (col. 2 lines 60-68). In some of the cultures obtained from untreated

Kawasaki syndrome patients, streptococcal pyrogenic exotoxins, SPE-B and C were also found (col. 3 lines 57-67). The invention the use of anti-toxic shock syndrome -1, anti-SPE-B or anti-SPE-C agents which can be administered to an infected subject (col. 7 lines 57-61). Modulation of the immune response can take several forms, such as administration of a mutated TSST-1 or mutated, non-pathogenic TSST-1 S. Aureus in a manner that elicits a protective immune response (col. 8 lines 4-10). The mutated forms refers to materials where some fundamental change has been made such as an addition, substitution or deletion of amino acids has occurred (col. 8 lines 29-36). Any of the materials can be used as vaccines, wherein the vaccines can include other materials such as an adjuvant (col. 87 lines 36-39).

Accordingly, it would have been obvious at the time of applicants invention to have used vaccines or pharmaceutical compositions comprising a mutated toxin as taught by Leung et al., wherein the toxin is SPE-C as taught by Goshorn et al., and Hartwig et al., because Leung et al., teaches that pharmaceutical compositions comprising mutant toxins is well known in the art and can modulate the immune response to provide protection against the bacterial pathogens.

Withdrawal of Rejections

5. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of applicants amendments and arguments.

6. Claims 1-10 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goshorn et al., in view of Kline et al., is withdrawn in view of applicants Declaration and arguments.

Response to Arguments

7. Applicant's arguments filed March 10, 2000 and March 13, 2000 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific amino acid mutations of Streptococcal pyrogenic exotoxin type C (SPE-C), does not reasonably provide enablement for altering the amino acid sequence by any insertion, deletion or substitution of one more amino acid. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims is maintained.

Applicants argue that the specification teaches 39 specific amino acid residues that are preferred sites for mutations. However, claim 1 is drawn to at least one amino acid change, therefore a mutant is be obtained by deletion, substitution or insertion of one or more amino acids, and this does not teach all amino acids changes that may or may not be changed without causing a detrimental effect to the SPE-C. The claims broadly teach at least one amino acid deletion, substitution or insertion, therefore any amino acid is being claimed, and no specific location for where the deletion, substitution or insertion or any combination thereof is recited, if all the amino acids are deleted or substituted or inserted the resulting mutant SPE-C could result in a mutant toxin not taught and/or enabled by the specification. The claims are also drawn to fragments of the mutant SPE-C, without any teaching as to fragment size, weight, or structural characteristics which would define fragments thereof.

The specification does not provide substantive evidence that the claimed vaccines which broadly teach the deletion, substitution or insertion of any amino acid is being claimed is capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing Streptococcus infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced by any mutant of SPE-C.

Applicant argues that they are entitled to a nonlethal SPE-C mutant which includes each of the 16 secondary structural features and 39 amino acid residues, however the claim 1 broadly recites a protein with a least one amino acid change, the claim does not recites the structural language which applicant argues.

The specification does not provide guidance on how multiple amino acids can be deleted, substituted or inserted for the production a stable bacterial SPE-C or fragments nor does the specification provide guidance on how any location can be used to produce a stable protein. No working examples are shown containing the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination thereof would result in the desired stable, active protein. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce a stable SPE-C toxin. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation and the rejection is maintained.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines

June 7, 2000

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641